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# PREPARATION AND EVALUATION OF SOME HYDROPHILIC PHENYLACETYL-PIPERAZINES AS PERIPHERALLY SELECTIVE κ-OPIOID RECEPTOR AGONISTS

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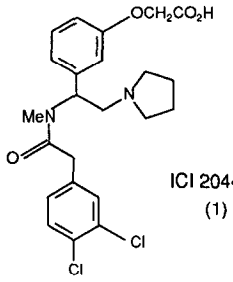
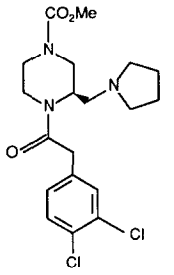
**Abstract** The synthesis of a series of hydrophilic phenylacetylpiperazines as potential peripherally selective κ-opioid receptor agonists is described. Several compounds were potent κ-agonists in vitro and one, the sulphone **(18)**, showed significant peripheral selectivity in vivo.

Three distinct opioid receptor sub-types (μ, κ and δ) have been characterised in the last 15 years[1]. The demonstration that κ-opioid receptors are involved in the control of nociception[2] has led to the proposal that agonists selective for this receptor could elicit analgesia whilst lacking the serious side-effects (e.g. addiction and respiratory depression) associated with morphine-like μ-agonists[3]. Although activation of κ-opioid receptors in the central nervous system is associated with undesirable side-effects, such as dysphoria and sedation, there is evidence suggesting that these receptors are also present on the peripheral terminals of primary afferent neurones[4]. A peripherally selective κ-agonist should attenuate the transmission of nociceptive information from these terminals and provide a novel analgesic with an improved side-effect profile.




ICI 204448
(1)

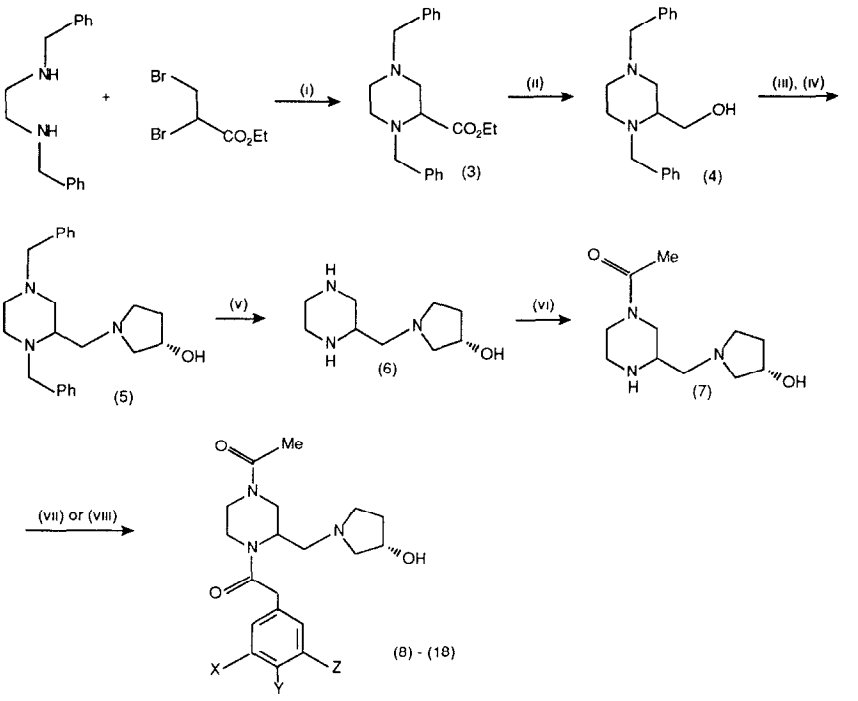



GR 103545
(2)

The phenoxyacetic acid ICI 204448 (1) has been identified as a κ-agonist which has limited access to the central nervous system[5], although a detailed analysis of its analgesic properties has not been carried out. We recently reported the synthesis of a series of phenylacetylpiperazines including GR 103545 (2) which are potent and selective κ-agonists[6]. This communication describes the synthesis of structurally related compounds which have retained κ-agonist activity, whilst their access to the central nervous system has been reduced.

We decided to prepare compounds which were less lipophilic than GR 103545 (2) (measured log D=3.14), to reduce blood-brain barrier penetration. Lipophilicity was reduced by replacing the N-methoxycarbonyl group of (2) by the more polar acetyl group and by the introduction of a 3-hydroxy group into the pyrrolidine ring. Selected substituents were then incorporated into the aromatic ring [phenylacetylpiperazines (8)-(18)] to provide a range of lipophilicities (measured log D between 1.25 and <-0.50).

**Scheme 1**

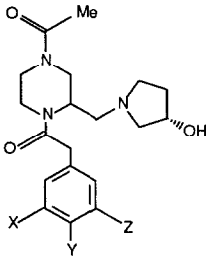



Reagents: (i) $Et_3N/PhCH_3/\Delta$, 92%; (ii) $LiAlH_4/THF/\Delta$, 94%; (iii) $SOCl_2/CHCl_3/\Delta$; (iv) MeCN/(S)-3-pyrrolidinol/Δ, 59%; (v) $H_2$/Pd-C/EtOH, 86%; (vi) $(MeCO)_2O$ (1.0 equiv)/$Et_3N/H_2O$, 89%; (vii) a) $ArCH_2CO_2H/CDI/CH_2Cl_2$, b) $LiOH/H_2O$/THF, 33-85%; (viii) $ArCOCl/Et_3N/CH_2Cl_2$, 56-71%.

The synthesis of compounds (8)-(18) is shown in Scheme 1. The alcohol (4) was converted to the corresponding chloride and aminated with (S)-3-pyrrolidinol[7,8], to provide the pyrrolidinylmethyl piperazine (5). Hydrogenolytic debenzylation was followed by the regioselective acetylation of the resultant triamine (6) to afford the acetamide (7), a key intermediate, in good yield. Subsequent acylation of (7) using the appropriate arylacetic acid or acid chloride[9] gave the required arylacetamides (8)-(18)[10].

The Compounds (8)-(18) (Table 1) were screened for <u>in vitro</u> agonist potency at the κ-receptor in the rabbit vas deferens (LVD)[11]. The more potent agonists ($IC_{50}$ <40nM) were further evaluated for antinociceptive activity <u>in vivo</u> using the mouse acetylcholine-induced abdominal constriction test[12]. The ratio of antinociceptive potencies for each compound on peripheral (subcutaneous; s.c.) and central (intracerebroventricular; i.c.v.) administration was determined. Since the action of κ-agonists in abdominal constriction is centrally mediated, a high $ED_{50}$ (s.c.) to $ED_{50}$ (i.c.v.) ratio indicates that a compound has restricted access into the central nervous system.

**Table 1. Biological Data for Phenylacetylpiperazines (8)-(18)**




| Compound | X | Y | Z | Measured Log D | LVD: $IC_{50}$,nM[a] | Mouse Ach-induced Abdominal Constriction $ED_{50}$ (mg/kg)[b] s.c. | i.c.v. | s.c./i.c.v. |
|---|---|---|---|---|---|---|---|---|
| GR103545 | | | | 3.1 | 0.02 | 0.0003 | 0.0002 | 1.5 |
| (8) | H | Cl | Cl | 1.2 | 0.22 | 0.7 | 0.007 | 100 |
| (9) | H | $CF_3$ | H | 1.0 | 1.5 | 0.76 | 0.008 | 95 |
| (10) | H | SMe | H | 0.6 | 37 | 1.52 | 0.075 | 20 |
| (11) | F | H | F | 0.3 | 4.6 | 2.5 | 0.006 | 417 |
| (12) | H | H | OMe | 0.0 | 49 | NT[c] | NT[c] | |
| (13) | H | $NO_2$ | H | 0.0 | 6.3 | 4.8 | 0.024 | 200 |
| (14) | H | OMe | H | -0.1 | 230 | NT | NT | |
| (15) | H | H | $NO_2$ | -0.1 | 14 | 0.74 | 0.006 | 123 |
| (16) | H | H | H | -0.1 | 400 | NT | NT | |
| (17) | H | SOMe | H | <-0.5 | 140 | NT | NT | |
| (18) | H | $SO_2Me$ | H | <-0.5 | 0.9 | 2.21 | 0.0008 | 2762 |
| ICI204448 | | | | 0.3[5] | 7.4 | 4.4 | 0.13 | 34 |

a) Figures quoted are the mean of two independent determinations typically with the individual values within ±10% of the mean.

b) n=6-12. A standard κ-agonist was used in each test and $ED_{50}$ values did not change significantly between tests.

c) NT = not tested

Many of the phenylacetylpiperazines were potent κ-agonists in vitro although none were as potent as GR103545 (2). No correlation was observed between lipophilicity and κ-agonist potency. In the mouse abdominal constriction model (i.c.v. route) the relative potencies of the compounds tested generally paralleled those observed in vitro. Whereas GR 103545 (2) was almost equipotent in vivo when administered by the peripheral or central routes, the new compounds showed significantly higher potency upon i.c.v. relative to s.c. administration. In particular, the sulphone (18) was almost 3000 times more potent when administered by the i.c.v. route. In conclusion, these results indicate that κ-agonist potency can be retained in more hydrophilic structures which have restricted access to the CNS. In particular, the sulphone (18) may represent an important lead towards identifying an effective analgesic with an improved side-effect profile.

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7. Prepared in 3 steps from (L)-Malic acid.
8. We have shown that compounds derived from (R)-3-pyrrolidinol in this and other series are less potent κ-agonists than those derived from the (S)-isomer (unpublished results).
9. Phenacetyl chlorides were used where commercially available. 4-(Methylthio)phenylacetic acid was prepared from thioanisole by acetylation followed by a modified Willgerodt reaction (J. Casanova, Jr., N.D. Werner and H.R. Kiefer, J.Am.Chem.Soc., 1967, 89, 2411) and was subsequently oxidised to give the corresponding sulphoxide and sulphone derivatives.
10. Satisfactory spectroscopic and microanalytical data was obtained for all final compounds.
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